THE CLAIMS

1. (currently amended) A method for treating a disease state in mammals caused by mammalian nasal and sinus cells involved in the inflammatory response comprising contacting the mammalian nasal and sinus cells with an inflammatory mediator; wherein the inflammatory mediator is present in an amount capable of reducing the undesired inflammatory response, is an antioxidant, and is selected from the group consisting of pyruvate and ~~a~~ pyruvate precursors, wherein the pyruvate precursor is not propylene glycol.

2. (original) The method according to claim 1, wherein the inflammatory mediator is formulated into nasal drops.

3. (original) The method according to claim 2, wherein the inflammatory mediator is formulated in a concentration of about 0.1mM to 10.0 mM.

4. (original) The method according to claim 1, wherein the inflammatory mediator is formulated into a nasal ointment.

5. (original) The method according to claim 4, wherein the inflammatory mediator is formulated in a concentration of 0.1mM to 10.0 mM.

6. (original) The method of claim 1, wherein the inflammatory response being reduced is at least one of the following: oxygen radical production, hydrogen peroxide production, cytokine and protease production, prostaglandin production, erythema, histamine and interleukin production.

7. (canceled)

8. (previously presented) The method of claim 1, wherein the inflammatory mediator is pyruvate.

9. (previously presented) The method of claim 8, wherein the pyruvate is selected from the group consisting of pyruvic acid, lithium pyruvate, sodium pyruvate, potassium pyruvate, magnesium pyruvate, calcium pyruvate, zinc pyruvate, manganese pyruvate, and mixtures thereof.

10. (previously presented) The method of claim 1, wherein the inflammatory mediator is a pyruvate precursor.

11. (previously presented) The method of claim 10, wherein the pyruvate precursor is selected from the group consisting of pyruvyl-glycene, pyruvyl-alanine, pyruvyl-leucine, pyruvyl cysteine, pyruvyl-valine, pyruvyl-isoleucine, pyruvyl-phenylalanine, pyruvamide, dihydroxyacetone, and salts of pyruvic acid.

12. (original) The method of claim 1, wherein the disease state is selected from the group consisting of rhinitis, eosiophilia syndrome, and sinusitis.

13. (original) The method of claim 1, further comprising contacting the mammalian nasal and sinus cells with a therapeutic agent.

14. (original) The method of claim 13, wherein the therapeutic agent is administered prior to the inflammatory mediator.

15. (original) The method of claim 13, wherein the therapeutic agent is administered concomitantly with administration of the inflammatory mediator.

16. (original) The method of claim 13, wherein the therapeutic agent is administered after administration of the inflammatory mediator.

17. (original) The method of claim 13, wherein the therapeutic agent is one or more agents selected from the group consisting of antibacterials, antivirals, antifungals, antihistamines, proteins, enzymes, hormones, nonsteroidal anti-inflammatories, cytokines, insulin, vitamins and steroids.

18. (original) The method of claim 13, wherein the therapeutic agent is oxymetazoline.

19. (withdrawn) A nasal solution, comprising:

a) water,

b) sodium chloride, 0.65% by weight,

c) pyruvate, at least 0.1mM,

d) buffer, and optionally

e) a preservative.

wherein the nasal moisturizing saline solution is buffered and made isotonic.

20. (withdrawn) The nasal solution of claim 19, wherein the pyruvate is present in the solution at a concentration between from about 0.1mM to about 10mM.

21. (withdrawn) The nasal solution of claim 19, wherein the pyruvate is present in the solution at a concentration between from about 0.5mM to about 10mM.

22. (withdrawn) The nasal solution of claim 19, wherein the buffer is selected from the group consisting of sodium bicarbonate, disodium phosphate/sodium phosphate, and monobasic potassium phosphate/sodium hydroxide.

23. (withdrawn) The nasal solution of claim 19, wherein the preservative is selected from the group consisting of phenylcarbinol, benzalkonium chloride, and thimerosal.

24. (withdrawn) The nasal solution of claim 19, wherein the pyruvate is present in the solution at a concentration of about 5mM, the buffer is sodium bicarbonate.

25. (withdrawn) The nasal solution of claim 19, further comprising a therapeutic agent wherein the therapeutic agent is one or more agents selected from the group consisting of antibacterials, antivirals, antifungals, antihistamines, proteins, enzymes, hormones, nonsteroidal anti-inflammatories, cytokines, insulin, vitamins and steroids.

26. (withdrawn) The method of claim 13, wherein the therapeutic agent is oxymetazoline.

27. (previously presented) A method for the treatment of rhinitis, eosinophilia syndrome, and sinusitis, comprising administering a nasal solution to the nostrils of a patient in need thereof, wherein the nasal moisturizing saline solution comprises:

a) water,
b) sodium chloride, 0.65% by weight,
c) pyruvate, at least 0.1mM,
d) buffer, and optionally
e) a preservative.

wherein the nasal moisturizing saline solution is buffered and made isotonic.

28. (original) The method of claim 27, wherein the pyruvate is present in the solution at a concentration between from about 0.1mM to about 10mM.

29. (original) The method of claim 27, wherein the buffer is selected from the group consisting of sodium bicarbonate, disodium phosphate/sodium phosphate, and monobasic potassium phosphate/sodium hydroxide.

29. (original) The method of claim 27, wherein the preservative is selected from the group consisting of phenylcarbinol, benzalkonium chloride, and thimerosal.

30. (original) The method of claim 27, wherein the pyruvate is present in the solution at a concentration of about 5mM, the buffer is sodium bicarbonate, and the preservative is phenylcarbinol.

31. (previously presented) The method of claim 13, wherein the therapeutic agent is an antibacterial.

RESPONSE

Claims 1-6 and 8-31 are pending, claims 19-26 are withdrawn subject to a restriction requirement, and claims 1-18 and 27-31 are rejected. Applicants have amended claim 1. Applicants have not deleted any claims and have not added any claims. Accordingly, claims 1-6, 8-18, and 27-31 are presently being examined.

In view of the following Amendment and Response, applicants respectfully request that the Examiner reconsider and withdraw the rejections made in the outstanding Office Action.

Support for the Amendments

Applicants have amended claim 1, and the claims dependent thereon, in order to more clearly describe and distinctly claim the subject matter of applicants' method for treating a disease state in mammals caused by mammalian nasal and sinus cells involved in the inflammatory response. Specifically, applicants have amended independent claim 1 to recite "wherein the pyruvate precursor is not propylene glycol." Applicants have further amended independent claim 1 to recite that the inflammatory mediator "is selected from the group consisting of pyruvate and pyruvate precursors.

These amendments to the claims are fully supported in the specification as originally filed, and thus no new matter is introduced by these amendments in accord with 35 U.S.C. Section 132. Accordingly, applicants request entry of these amendments.

Restriction Requirement of the Claims

The Examiner has acknowledged applicant's election with traverse of Group I. The Examiner states that applicants' arguments that searching all presented inventions would not represent an undue burden is not persuasive because the presented inventions encompass a large therapeutic compound group not linked by structure, medicament class or biochemical effect and to search this broad

functionally would place an undue burden on the Examiner. The Examiner has made the requirement final. The Examiner has withdrawn claims 19-26 from consideration.

Withdrawal of Rejection of Claims under 35 U.S.C. Section 112, first and second paragraphs.

Applicants acknowledge with appreciation that the Examiner has withdrawn the rejection of the claims under 35 U.S.C. Section 112, first and second paragraphs.

Withdrawal of Objection to the Specification under 35 U.S.C. Section 112, first paragraph.

Applicants acknowledge with appreciation that the Examiner has withdrawn the objection to the specification under 35 U.S.C. Section 112, first paragraph.

Rejection of Claims 1-12 and 27-31 under 35 U.S.C. Section 103 as being unpatentable over *Pandse et al.*, *Robinson*, and *Katz* in view of *Lindstrom et al* and *Lueck*.

The Examiner has issued a new rejection of claims 1-12 and 27-31 under 35 U.S.C. Section 103 as being unpatentable over CA 93:179735 (*Pandse et al.*), United States patent no. 3,666,801 (*Robinson*), and United States patent no. 5,798,388 (*Katz*), in view of United States patent no. 4,696,917 (*Lindstrom et al*) and Erich Lueck (Springer-Verlag, 1980, pages 263-264) (*Lueck*). The Examiner states that *Pandse et al.*, *Robinson*, and *Katz* teach the claimed compounds as old and well known in combination with various pharmaceutical carriers and excipients and as useful for treating inflammation. The Examiner argues that possessing these teachings, the skilled artisan would have been motivated to employ these

compounds for any anti-inflammatory use and enjoy a reasonable expectation of therapeutic success.

The Examiner states that claims 1-12 and 27-31 and the primary references differ as to recitation of salts or related compounds; the concomitant employment of these medicaments and carriers; nasal administration of the medicaments; and disclosure of antimicrobial activity of the active agent. The Examiner contends that it is obvious to combine therapeutic compounds, carriers, and excipients, each of which is taught by the prior art to be useful for the same purpose, in order to form a composition which is to be used for the very same purpose. The Examiner states that *Lindstrom et al.* teach the excipients herein claimed as useful in formulating anti-inflammatory medicaments; *Katz* teaches the claimed compounds for treating inflammation in body cavities and organs (nasal compositions); and *Lueck* teaches the active agent polyethylene glycol as possessing antimicrobial activity.

The Examiner states that the instant claims read on employing a pyruvate precursor to treat the instant disease state. The Examiner argues that he set forth propylene glycol as a pyruvate precursor a textual reference to teach this bio-conversion and argues that the skilled artisan would be charged with this knowledge and that propylene glycol possesses anti-inflammatory activity thus rendering the instant claims obvious over the prior art of record. The Examiner states that absent a negative limitation the skilled artisan would have seen this compound as obviating the claims and moreover the instant claims fail to provide for a minimum effective level of therapeutic activity to practice the instant claims. Thus, the Examiner argues that an agent possessing a scintilla of therapeutic activity would meet the activity requirements of the presented claims. Applicants' claims as amended obviate the Examiner's rejection.

In summary, applicants submit that the present claims, as amended, are not obvious over *Pandse et al.*, *Robinson*, and *Katz* in view of *Lindstrom et al.* and *Lueck*. As set out above, applicants have amended independent claim 1 to recite that the pyruvate precursor is not propylene glycol. Moreover, applicants have provided a minimum effective level of therapeutic activity to practice the instant claims. Specifically, applicants' claim 1 recites "wherein the inflammatory

mediator is present in an amount capable of reducing the undesired inflammatory response".

As set out in applicants' previous Response, applicants have amended claim 11 to delete "propylene glycol". Accordingly, *Pandse et al.* does not teach or suggest applicants' inflammatory mediator selected from the group consisting of pyruvate and a pyruvate precursor. Moreover, *Katz* teaches the use of pyruvate in lungs and does not teach the use of pyruvate for all cavities. Pyruvate acts differently in nasal cavities than in lungs. Accordingly, the combination of *Pandse et al.* and *Katz* do not provide applicants' method for treating a disease state in mammals caused by mammalian nasal and sinus cells involved in the inflammatory response comprising contacting the mammalian nasal and sinus cells with an inflammatory mediator. Applicants wish to note that they are unaware of any attempts by the Examiner to obtain prior art references.

The present invention provides a method for treating a disease state in mammals caused by mammalian nasal and sinus cells involved in the inflammatory response. The method comprises contacting the mammalian nasal and sinus cells with an inflammatory mediator. The inflammatory mediator is present in an amount capable of reducing the undesired inflammatory response and is an antioxidant. The inflammatory mediator is selected from the group consisting of pyruvate and pyruvate precursors.

The present invention also provides a method for the treatment of rhinitis, eosinophilia syndrome, and sinusitis and related conditions associated with nasal congestion. The method comprises administering a nasal solution to the nostrils of a patient in need thereof. The nasal moisturizing saline solution comprises water; sodium chloride, 0.65% by weight; pyruvate, at least 0.1mM; buffer; and optionally a preservative. The nasal moisturizing saline solution is buffered and made isotonic.

The *Pandse et al.* reference discloses the anti-inflammatory activity of propylene glycol. Propylene glycol is said to show anti-inflammatory activity in carrageenin inflammations. When compared with dexamethasone and phenylbutazone, propylene glycol is said to show approximately similar anti-inflammatory potency.

The *Robinson* reference discloses hydrazones of pyruvic acid and states that the compounds are anti-inflammatory agents. The compounds are prepared by reaction of the appropriate pyruvate with 4-tert-butylphenylhydrazine. The anti-inflammatory utility of the present compounds is said to be evident from the results of a standardized test for their capacity to inhibit the formation of granuloma induced in adrenalectomized rats by implanted cotton.

The *Katz* reference discloses a method for treating asthma in mammals caused by mammalian cells involved in the inflammatory response. The method comprises contacting the mammalian cells with an inflammatory mediator. The inflammatory mediator is an antioxidant and is selected from the group consisting of pyruvate and a pyruvate precursor. The inflammatory mediator is present in an amount capable of reducing the undesired inflammatory response and is not administered together with albuterol.

The *Lindstrom et al.* reference discloses a composition for irrigating and flushing body tissue during surgery. The composition comprises Eagle's Minimum Essential Medium with Earle's salts, without L-glutamine and phenol red, and supplemented with non-essential amino acids; chondroitin sulfate; a buffer system based on N'-2-hydroxyethylpiperazine-N'ethane sulfonic acid; 2-mercaptoethanol; and a pyruvate.

The *Lueck* reference discloses 1,2-propylene glycol has a preservative action and is excreted from the body partly unchanged and partly oxidized to lactic acid. The antimicrobial action, like that of sodium chloride and sucrose, is based on a reduction in the water activity.

Applicants have enclosed copies of the following 7 references:

Ann Allergy; 1988 Oct;61(4):305-10; Comparative tolerability of two formulations of Rhinalar (flunisolide) nasal spray in patients with seasonal allergic rhiniti; Greenbaum J, Leznoff A, Schulz J, Mazza J, Tobe A, Miller D.

Food Chem Toxicol; 1989 Sep;27(9):573-83; Subchronic nose-only inhalation study of propylene glycol in Sprague-Dawley rats; Suber RL, Deskin R, Nikiforov I, Fouillet X, Coggins CR.

Res Exp Med (Berl); 1989: 189:39-42. Effect of Propylene glycol on, redox state of the perfused rat liver, a note of caution; Scholmerich J, Kitamura S., Miyai K.

Crit Rev Toxicol; 1999 Jul;29(4):331-65. A review of the comparative mammalian toxicity of ethylene glycol and propylene glycol; LaKind JS, McKenna EA, Hubner RP, Tardiff RG.

J Am Vet Med Assoc; 1990 Jun 1;196(11):1816-9. Effects of propylene glycol-containing diets on acetaminophen-induced methemoglobinemia in cats; Weiss DJ, McClay CD, Christopher MM, Murphy M, Perman V.

Pharmacotherapy; 1996 Jul-Aug;16(4):690-3; Propylene glycol: the safe diluent that continues to cause harm; Glover Ml, Reed MD.

Biochem Med Metab Biol; 1989 Oct;42(2):87-94; Kinetics of oral propylene glycol-induced acute hyperlactatemia; Morshed KM, Nagpaul JP, Majumdar S, Amma MK.

These references show that propylene glycol is toxic in lungs and nasal cavities and causes hemorrhage, dehydration, and pain. As set out above, applicants have amended independent claim 1 to recite that the pyruvate precursor is not propylene glycol. Glycols are antimicrobials because they dissolve membranes and coat microorganisms and do not allow microorganisms to attach to mucus membranes. Unlike glycol, pyruvate is not an antimicrobial. Unlike pyruvate, propylene glycol is not an antioxidant, is not transported into cells, cannot protect cells and DNA, and is irritating to the skin.

Applicants further submit that *Pandse et al.* and *Katz* do not teach the use of pyruvate for all cavities. *Katz* teaches the use of pyruvate in lungs. Pyruvate acts differently in nasal cavities than in lungs. Nasal cavities produce 1000 times more nitric oxide than lungs. This amount of nitric oxide production in the lungs can damage lung tissue. Pyruvate reduces levels of nitric oxide and hydrogen peroxide. Glycols do not reduce levels of nitric oxide and hydrogen peroxide.

Lindstrom et al. merely uses pyruvate for irrigation solutions for ATP. *Lindstrom et al.* does not disclose that pyruvate is an antioxidant that reduces nitric oxide and reduces inflammatory mediators such as proteases and cytokines. *Lindstrom et al.* does not teach the use of pyruvate in the lungs or sinuses.

Carrageenin is a polysaccharide of red seaweed and can cause inflammation in man. Propylene glycol inhibits the inflammation caused by carrageenin by coating carrageenin to reduce contact with mucosa. Unlike propylene glycol, pyruvate is not a solvent that reduces carrageenin induced inflammation.

Accordingly, the Examiner's rejection of claims 1-12 and 27-31 under 35 U.S.C. Section 103 as being unpatentable over *Pandse et al.*, *Robinson*, and *Katz* in view of *Lindstrom et al* and *Lueck* should be withdrawn.

Rejection of Claims 10-12 under 35 U.S.C. Section 103 as being unpatentable over *Pandse et al.* and *Robinson* in view of the *Merck Index*.

The Examiner has rejected claims 10-12 under 35 U.S.C. Section 103 as being unpatentable over *Pandse et al.* and *Robinson* in view of the *Merck Index (7756)*. The Examiner states that *Pandse et al.* and *Robinson* teach the claimed compounds as old and well known in combination with various pharmaceutical carriers and excipients. The Examiner states that claims 10-12 and the primary references differ as to the recitation of metabolite compounds; and the nasal administration of the medicaments. The Examiner argues that the *Merck Index (7756)* teaches the claimed pyruvate as the degradation product of propylene glycol, motivating the skilled artisan to employ this compound, or its degradation products for the same anti-inflammatory use. The Examiner states that *Pandse et al.* and *Robinson* teach the claimed compounds for treating inflammation generally, and not limited to one specific anti-inflammatory use. The Examiner concludes that the skilled artisan would have been motivated to employ the claimed anti-inflammatory compounds for nasal administration and enjoy a reasonable expectation of therapeutic success, absent information to the contrary. Applicants' claims as amended obviate the Examiner's rejection.

As set out above, applicants have amended independent claim 1 to recite that the pyruvate precursor is not propylene glycol. The combination of the primary reference of *Pandse et al.* and *Robinson* with the secondary reference of *Merck Index (7756)* does not disclose applicants' method for treating a disease state in mammals caused by mammalian nasal and sinus cells involved in the

inflammatory response. Because the primary references of *Pandse et al.* and *Robinson* do not teach or suggest applicants' method for treating a disease state in mammals caused by mammalian nasal and sinus cells, the secondary reference of *Merck Index (7756)*, adds nothing to the primary references of *Pandse et al.* and *Robinson*. *Pandse et al.* and *Robinson* do not disclose applicants' method for treating a disease state in mammals caused by mammalian nasal and sinus cells.

Accordingly, the Examiner's rejection of claims 10-12 under 35 U.S.C. Section 103 as being unpatentable over *Pandse et al.* and *Robinson* in view of the *Merck Index (7756)* should be withdrawn.

Rejection of Claims 13-18 under 35 U.S.C. Section 103 as being unpatentable over *Pandse et al.*, *Robinson*, and *Katz* in view of *Lindstrom et al.* and *Lueck* in further view of *Hummel et al.*

The Examiner has rejected claims 13-18 under 35 U.S.C. Section 103 as being unpatentable over *Pandse et al.*, *Robinson*, and *Katz* in view of *Lindstrom et al.* and *Lueck*, as set forth above, in further view of 130:163132 (*Hummel et al.*) The Examiner states that *Hummel et al.* teaches that oxymetazoline is old and well known in combination with various pharmaceutical carriers and excipients in a dosage form, and is taught as useful for treating rhinitis. The Examiner states that claims 13-18 and the primary references differ as to the concomitant employment of these medicaments and carriers. The Examiner argues that it is obvious to combine therapeutic compounds, carriers and excipients each of which is taught by the prior art to be useful for the same purpose, in order to form a composition which is to be used for the very same purpose. Applicants traverse the Examiner's rejections.

The combination of the primary references of *Pandse et al.* and *Robinson* with the secondary reference of *Hummel et al.* does not disclose applicants' method for treating a disease state in mammals caused by mammalian nasal and sinus cells involved in the inflammatory response. Because the primary reference of *Pandse et al.* and *Robinson* do not teach or suggest applicants' method for treating a disease state in mammals caused by mammalian nasal and sinus cells, the secondary reference of *Hummel et al.*, adds nothing to the primary references of *Pandse et al.*

and *Robinson*. *Pandse et al.* and *Robinson* do not disclose applicants' method for treating a disease state in mammals caused by mammalian nasal and sinus cells.

Accordingly, the Examiner's rejection of claims 13-18 under 35 U.S.C. Section 103 as being unpatentable over *Pandse et al.*, *Robinson*, and *Katz* in view of *Lindstrom et al.* and *Lueck*, as set forth above, in further view of *Hummel et al.* should be withdrawn.

Obviousness of a composition or process must be predicated on something more than it would be obvious "to try" the particular component recited in the claims or the possibility it will be considered in the future, having been neglected in the past. *Ex parte Argabright et al.* (POBA 1967) 161 U.S.P.Q. 703. There is usually an element of "obvious to try" in any research endeavor, since such research is not undertaken with complete blindness but with some semblance of a chance of success. "Obvious to try" is not a valid test of patentability. *In re Mercier* (CCPA 1975) 515 F2d 1161, 185 U.S.P.Q. 774; *Hybritech Inc. v. Monoclonal Antibodies. Inc.* (CAFC 1986) 802 F2d 1367, 231 U.S.P.Q. 81; *Ex parte Old* (BPAI 1985) 229 U.S.P.Q. 196; *In re Geiger* (CAFC 1987) 815 F2d 686, 2 U.S.P.Q.2d 1276. *In re Dow Chemical Co.* (CAFC 1988) F2d, 5 U.S.P.Q.2d 1529. Patentability determinations based on that as a test are contrary to statute. *In re Antonie* (CCPA 1977) 559 F2d 618, 195 U.S.P.Q. 6; *In re Goodwin et al.* (CCPA 1978) 576 F2d 375, 198 U.S.P.Q. 1; *In re Tomlinson et al.* (CCPA 1966) 363 F2d 928, 150 U.S.P.Q. 623. A rejection based on the opinion of the Examiner that it would be "obvious to try the chemical used in the claimed process which imparted novelty to the process does not meet the requirement of the statute (35 U.S.C. 103) that the issue of obviousness be based on the subject matter as a whole. *In re Dien* (CCPA 1967) 371 F2d 886, 152 U.S.P.Q. 550; *In re Wiaains* (CCPA 1968) 397 F2d 356, 158 U.S.P.Q. 199; *In re Yates* (CCPA 1981) 663 F2d 1054, 211 U.S.P.Q. 1149. Arguing that mere routine experimentation was involved overlooks the second sentence of 35 USC 103. *In re Saether* (CCPA 1974) 492 F2d 849,181 U.S.P.Q. 36. The issue is whether the experimentation is within the teachings of the prior art. *In re Waymouth et al.* (CCPA 1974) 499 F2d 1273, 182 U.S.P.Q. 290. The fact that the prior art does not lead one skilled in the